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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HISSONG, BRUCE D	
ART UNIT	**PAPER NUMBER**
1646	

NOTIFICATION DATE	DELIVERY MODE
02/08/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/693,657	CHEMTOB ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,18 and 38-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12, 18, 38-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicants' response to the office action mailed on 4/30/2007, including arguments/remarks and amendments to the claims and specification, was received on 11/1/2007 and has been entered into the record.

2. In the response received on 11/1/2007, the Applicants cancelled claims 1-11, 13-17, and 19-27, and added new claims 38-41. Therefore, claims 12, 18, and 39-41 are currently pending and are the subject of this office action.

Specification

Objection to the specification for recitation of sequences without sequence identifiers, as set forth on page 3 of the office action mailed on 4/30/2007, is *withdrawn* in response to Applicants' amendments to the specification to include appropriate sequence identifiers.

Claim Objections

1. Objection to claim 12, as set forth on page 3 of the office action mailed on 4/30/2007, is *withdrawn* in view of Applicants' amendments to the claim to recite "a peptide of 5 to 20 amino acids".

2. The Examiner suggests the syntax of claim 18 can be improved by amending the phrase "peptide inhibiting" to "peptide-inhibiting".

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection maintained

Claims 12 and 18 *remain rejected*, and new dependent claims 38-41 are also rejected under 35 USC § 112, first paragraph, regarding lack of enablement for VEGFR peptide antagonists other than SEQ ID NO: 2, as set forth on pages 3-6 of the office action mailed on 4/30/2007.

The claims of the invention are drawn to a non-competitive extracellular cytokine receptor antagonist, wherein said antagonist is a peptide of 5 to 20 amino acids, and wherein said peptide comprises a sequence that, over its full length, is at least 82% identical to the amino acid sequence of SEQ ID NO: 2, and wherein this peptide antagonist inhibits proliferation and/or neovascularization in cells contacted with said peptide. The claims further drawn to said peptide antagonist wherein it comprises a sequence that contains a substitution, deletion, or addition of one amino acid sequence in the sequence of SEQ DI NO: 2, and an antagonist consisting of the sequence of SEQ ID NO: 2. Finally, the claims are drawn to methods of inhibiting human VEGF activity in a cell by contacting a cell with the claimed peptide antagonist.

In the response received on 11/1/2007, the Applicants argue that the claims have been amended to recite only peptide antagonists having from 5 to 20 amino acids and exhibiting 82% homology with SEQ ID NO: 2, and being able to inhibit cell proliferation and/or neovascularization, and thus the claimed peptide antagonists are structurally related to SEQ ID NO: 2 and are required to share biological function with SEQ ID NO: 2. The Applicants also argue that the specification provides *in vitro* assays for determining the function of a peptide antagonist, and that creation of peptides that are commensurate in scope with the claims is standard in the art. Therefore, the specification provides adequate guidance for a person of ordinary skill in the art to make and use the claimed peptides and practice the claimed methods.

These arguments have been fully considered and are not persuasive. Although the amendments to the claims have narrowed the breadth of the claimed subject matter, the breadth of the claims is still excessive in that the claims read on any 5 to 20 amino acid peptide that is only 82% identical to SEQ ID NO: 2. Although a person of ordinary skill in the art could easily determine which 2 amino acids out of the 10 present in SEQ ID NO: 2 could be changed to produce a peptide that is 82% identical to SEQ ID NO: 2, the skilled artisan would not envision how to make a peptide of only 5 amino acids that is 82% identical to SEQ ID NO: 2, or a peptide of 20 amino acids that is 82% identical to SEQ ID NO: 2. There is no guidance or examples in the specification which teach which amino acids can be added to the peptide of SEQ ID NO: 2, as in the case of peptides having 20 amino acids, or deleted from SEQ ID NO: 2, as in the case of peptides having only 5 amino acids. The claims read on peptides having only 5 amino acids; however, one of ordinary skill in the art would not predict which 5 amino acids of SEQ ID NO: 2

(which is 10 amino acids) could be deleted. Similarly, a skilled artisan would not be able to predict which amino acids or peptides could be added to SEQ ID NO: 2 to create a peptide that is 20 amino acids because the skilled artisan would know that addition of extra amino acids could change the tertiary conformation of the claimed peptide, thus rendering it unable to inhibit VEGF-induced proliferation. Such predictions would require further, undue experimentation, especially in view of the teachings of Mickle *et al*, which highlight the unpredictability in predicting a protein's function after mutation.

Furthermore, the claims require the claimed peptides to be able to decrease cell proliferation and/or neovascularization. As written, the claims read broadly on inhibition of all types of cellular proliferation. The specification provides guidance and examples showing that the peptide of SEQ ID NO: 2 can inhibit VEGF-induced proliferation, but there is no guidance or examples which teach inhibition of cellular proliferation in response to any other stimulus. It is known in the art that cells can proliferate in response to many types of stimuli. For example, activated $CD4^+$ T cells proliferate in response to interleukin (IL)-2 (Mohamed-Habib et al, J. Immunol., 1987, Vol. 139(2), pages 443-451). A person of ordinary skill in the art, however, would not predict that inhibition of VEGF signaling would inhibit cell proliferation in response to IL-2, or any stimulus other than VEGF, and therefore one of skill in the art would not be able to make and use the claimed peptides for inhibiting all types of cellular proliferation.

Therefore, due to the breadth of the claims, which read on all possible peptides from 5 to 20 amino acids which are only 82% identical to SEQ ID NO: 2 that are capable of inhibiting all types of cellular proliferation, the lack of guidance and examples showing which amino acid residues could be deleted, substituted, or added, and the unpredictability in the art regarding retention of biological function after such modifications, one of ordinary skill in the art would require further, undue experimentation in order to make and use any peptide antagonists, other than SEQ ID NO: 2, which are capable of inhibiting any type of proliferation other than VEGF-induced proliferation. It is noted that claims 38-41 are rejected for depending from rejected base claims.

Claim Rejections - 35 USC § 112, first paragraph - written description

Rejection maintained

Claims 12 and 18 *remain rejected*, and new dependent claims 38-41 are also rejected under 35 USC § 112, first paragraph, regarding lack of written description for VEGFR peptide antagonists other than SEQ ID NO: 2, as set forth on pages 6-7 of the office action mailed on 4/30/2007.

The subject matter of the instant invention is discussed *supra*. In the response received on 11/1/2007, the Applicants argue that the claims now recite peptides that are structurally related to a specific sequence, SEQ ID NO: 2, and recite the functional limitation of inhibiting cell proliferation and/or neovascularization. The Applicants also assert that the specification describes a peptide, SEQ ID NO: 2, that is capable of inhibiting VEGF-induced cell proliferation. Furthermore, the Applicants argue that the specification states that the claimed peptides can be derived from SEQ ID NO: 2 via "substitutions, deletions, or additions of one or more amino acids, provided that the biological activity of the protein is conserved".

These arguments have been fully considered and are not persuasive. The claims read on all possible peptides of 5 to 20 amino acids, wherein said peptides comprise a sequence that is 82% identical to SEQ ID NO: 2. Given the broadest reasonable interpretation, the claims read on peptides comprised of SEQ ID NO: 2 and up to 10 additional amino acids, or peptides consisting only of 5 of the 10 possible amino acid residues of SEQ ID NO: 2. The specification describes a peptide, SEQ ID NO: 2, that is capable of inhibiting VEGF-induced cell proliferation and neovascularization, but does not describe any other peptide(s) exhibiting these biological activities. Furthermore, the specification does not describe which core 5 amino acid residues of SEQ ID NO: 2 would be minimally required to conserve this function, or which amino acid residues or peptides could be added to SEQ ID NO: 2 and produce a peptide with the desired biological activity. The specification also does not describe which amino acid residues of SEQ ID NO: 2 which could be mutated in order to create a peptide that is 82% identical to SEQ ID NO: 2 with biological activity. For these reasons, the specification does not provide adequate written description of the claimed genus of all possible peptides from 5 to 20 amino acids which comprise a peptide having only 82% identity to SEQ ID NO: 2. It is noted that claims 38-41 are rejected for depending from rejected base claims.

Rejection necessitated by amendment

Claim 12, 18, and 38-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claims 12 and 18 recite the limitation that the claimed peptides are "at least 82% identical" to the amino acid sequence of SEQ ID NO: 2. After extensive review, the Examiner is unable to find, in the

Specification as originally filed, support for this newly added limitation in the claim. This newly added limitation is not expressly asserted, nor does it flow naturally from the specification as originally filed. The Examiner notes that the Applicants state that support for this limitation is found at, for example, paragraph 0041, which states that rat and horse VEGFR protein sequences are 82% similar to human VEGFR. However, the claims do not read on VEGFR, but are instead drawn to specific peptide inhibitors of VEGFR. There is no disclosure in the specification which expressly asserts peptides with 82% *to SEQ ID NO: 2*, nor does this limitation flow naturally from the specification. Accordingly, the inclusion of this new limitation into the claims represents new matter.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Rejections withdrawn

1. Rejection of claim 18 under 35 USC § 112, second paragraph, as being indefinite regarding the acronym VEGFR, as set forth on page 8 of the office action mailed on 4/30/2007, is *withdrawn* in response to Applicants' amendments to the claims to define the acronym upon it's first use.

2. Rejection of claim 18 under 35 USC § 112, second paragraph, as being indefinite regarding the metes and bounds of inhibiting VEGF "activity", as set forth on page 8 of the office action mailed on 4/30/2007, is *withdrawn* in response to Applicants' amendments to the claims to specifically recite inhibition of cell proliferation and inhibition of neovascularization.

3. Rejection of claim 18 under 35 USC § 112, second paragraph, as being indefinite for omitting essential method steps regarding "targeting" VEGRF with an antagonist, as set forth on pages 8-9 of the office action mailed on 4/30/2007, is *withdrawn* in response to Applicants' amendments to the claims to recite contacting a cell with the claimed peptide antagonist, and the inclusion of a limitation which requires a decrease in proliferation of said cell relative to a control cell not contacted with said peptide.

Rejection necessitated by amendment

Claims 12, 18, and 38-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12 and 18 recite a peptide of 5 to 20 amino acids, wherein said peptide comprises a sequence that, over its full length, is at least 82% identical to the sequence of SEQ ID NO: 2. As written, the claims read on peptides 5-7 amino acids in length. It is not clear, however, how a peptide of only 5-7 amino acids can be 82% identical to the 10 amino acid sequence of SEQ ID NO: 2. Likewise, it is not clear how a peptide of 20 amino acids can be 82% percent identical to a peptide of 10 amino acids. It is noted that claims 38-41 are rejected for depending from rejected base claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Rejections withdrawn

Rejection of claim 12 under 35 USC § 102(b) as being anticipated by either Tan *et al*, Binetruy-Tournaire *et al*, Thomas *et al*, or Davis-Smyth *et al*, as set forth on pages 9-12 of the office action mailed on 4/30/2007, is *withdrawn* in response to Applicants' amendments to the claims to recite a peptide of 5 to 20 amino acids, wherein said peptide comprises a sequence that is 82% identical to SEQ ID NO: 2. It is noted that neither Tan *et al*, Binetruy-Tournaire *et al*, Thomas *et al*, nor Davis-Smyth *et al* teach peptides with only 5 to 20 amino acids, wherein these peptides are at least 82% identical to SEQ ID NO: 2.

Conclusion

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
Art Unit 1646

/Robert Landsman/
Primary Examiner, Art Unit 1647